## **End of Result Set**

# Generate Collection

L1: Entry 1 of 1

File: USPT

Jul 18, 2000

115 08/809,455 US-PAT-NO: 6090916 DOCUMENT-IDENTIFIER: US 6090916 A

TITLE: Nematode-extracted serine protease inhibitors and anticoagulant proteins

DATE-ISSUED: July 18, 2000

### INVENTOR-INFORMATION:

| NAME                             | CITY             | STATE                 | ZIP CODE | COUNTRY |
|----------------------------------|------------------|-----------------------|----------|---------|
| Vlasuk; George Phillip           | Carlsbad         | 2.54                  | N'A      | M/A     |
| Stanssens; Fatrick Eric Hugo     | St-Martens-Latem | N A                   | N'A      | BEX     |
| Messens; Joris Hilda Lieven      | Dilbeek          | $\mathbb{R}^{-}A$     | N'A      | BEX     |
| Lauwereys; Marc Josef            | Haaltert         | N A                   | ∏ A      | BEX     |
| LaRoche; Yves Rene               | Brussels         | N A                   | N A      | BEX     |
| Jespers; Laurent Stephane        | Tervaren         | $A \cdot \mathcal{U}$ | Ν Ά      | BEX     |
| Gansemans; Yannick Georges Jozef | Ichtegem         | N A                   | N-A      | BEX     |
| Miyle; Matthew                   | Boulder          | CD                    | N A      | N/A     |
| Bergum; Peter W.                 | San Diego        | CA                    | N - A    | N/A     |

US-CL-CUFRENT: <u>530/350</u>

#### CLAIMS:

#### We claim:

1. An isolated protein having anticoagulant activity, including factor Xa inhibitory activity, and having one or more NAP domains, where each NAP domain includes the sequence:

Cys-Al-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 (Formula II), wherein

- (a) All is an amino acid sequence of 7 to 8 amino acid restriues;
- (b) Al is an amino acid sequence;
- (b) Ab is an amino abid sequence of 3 amino abid residues;
- (d) A4 is an amino acid sequence;
- (e) At is an amine acid sequence of 3 to 4 amino acid residues;
- (f) A6 is an amino acid sequence;
- (q) A7 is an amino acid residue;
- (h) A8 is an amino acid sequence of 11 to 12 amino acid residues;
- (i) A9 is an amine acid sequence of 5 to 7 amino acid residues; and
- (j) All is an amino acid sequence;

wherein each A2, A4, A6 and A11 has an independently selected number of independently selected amino acid residues and each sequence is selected such that each NAP domain has in total less than about 120 amino acid residues and wherein said NAP domain includes the amino acid sequence:

Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 wherein

- (a: Cys-Al is selected from SEQ.ID.NOS. 67 and 156;
- (t) Cys-A2-Cys is selected from one of SEQ.ID.MOS. 157 to 159;
- (a) AS-Cys-A4 is selected from one of SEQ.ID.NOS. 160 to 173;

- (d) Cys-AE is selected from SEQ.II.Not. 174 and 175;
  (e) Cys-AE is selected from SEQ.II.Not. 174 and 175;
  (e) Cys-AE is selected from one if VE..II.NoS. 176 to 176;
  (f) Cys-AF-Cys-AE is selected from JE..II.Not. 175 and 186;
  (g) Cys-AE is selected from the JE.EI.Not. 181 to 186; and TE. Cys-AII is selected from the JE.EI.Not. 184 to 184.

```
2. An isolated protein having anticoagulant activity, including factor VIIa-TF
inhibitory activity, and having one or more MAP domains wherein each MAP domain
includes the sequence:
Oys-A1-Dys-A2-Cys-A3-Dys-A4-Dys-A5-Dys-A6-Dys-A7-Dys-A6-Dys-A9-Dys-A9-Cys-A10 (FORMULA III ,
wherein
(a) All is an amino acid sequence of 7 to 8 amino acid residues;
(b) A2 is an amino acid sequence;
(a) A3 is an amino acid sequence of 3 amino acid residues;
(d) A4 is an amino acid sequence;
(e) A5 is an amine acid sequence of 3 to 4 amine acid residues;
(f) Ab is an amine acid sequence;
(g) A7 is an amino acid residue;
(n) A3 is an amino acid sequence of 11 to 12 amino acid residues; (i) A3 is an amino acid sequence of 5 to 7 amino acid residues; and
(j) AlO is an amino acid sequence;
wherein each of Al, A4, A6 and All has an independently selected number of
independently selected amino acid residues and wach sequence is selected such that
each NAP domain has in total less than about 121 amino abid residues, and wherein
said NAP immain includes the amint acid sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A6-Cys-A6-Cys-A6-Cys-A5-Cys-A5-Cys-A9-Cys-A10
wherein
(a) Cys-Al is selected from SEQ.ID.NOS. 68 and LD5;
(b) Cys-A2-Cys is selected from one of SEQ.10.NOS. 206 to 208;
(a) A3-Cys-A4 is selected from one of SEQ.ID.NOS. 209 to 222;
(d) Cys-A5 is selected from SEQ.ID.NOS. 023 and 204;

    (e) Cys-A6 is selected from one of SEQ.ID.NOS. 128 to 007;
    (f) Cys-A7-Dys-A8 is selected from one of SEQ.ID.NOS. 218 to 229;

(g) Cys-A9 is selected from one of SEQ.10.NOS. 130 to 152; and
(n) Cys-Al0 is selected from one of SEQ.10.NOS. 355 to 185.
3. An isolated protein having serine protease inhibitory activity and having one or
more NAP domains, wherein each NAP domain includes the sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 (FORMULA IV),
wherein
(a) Al is an amino acid sequence of 7 to 8 amino acid residues;
(b) Al is an amint abid sequence;
(c) A3 is an amint acid sequence of 3 amino acid residues;
(d) A4 is an amint abid sequence;
(e) AS is an amin: adid sequence of 3 to 4 amino anid evaluaes;
(f) A@ is an amint acid sequence;
(g) A7 is an amino acid residue;
(\hat{\mathbf{n}}) A8 is an amino acid sequence of 10 to 10 amono acid residues;
(i) A9 is an amino acid sequence of \tilde{\epsilon} to 7 amino acid residues; and
(j) AlO is an amino acid sequence;
wherein each of A2, A4, A6 and A10 has an independently selected number of
independently selected amino acid residues and each sequence is selected such that
each NAP domain has in total less than about 120 amino acid residues, and wherein
said MAP domain includes the amino acid sequence:
Cys-A1-Cys-A1-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10, wherein
(a) Cys-Al is selected from SEQ.IE.NOS. 96 and 254;
(b) Cys-Al-Cys is selected from one of SEQ.ID.NO3. 285 to 287;
(a) A3-Cys-A4 is selected from one of SEQ.ID.NOS. 258 to 271;
(d) Cys-A5 is selected from SEQ.ID.NOS. 172 and 2
(e) Cys-A6 is selected from SEQ.II.NOS. 174 to 2
(f) Cys-AC-Cys-A8 is selected from one of SEQ.ID.NOS. 077 to 279;
(g) Cys-A0 is selected from one of SEQ.ID.NOS. 280 to 282; and
(h) Cys-All is selected from one of SEQ.ID.NOS. 3-5 to 307.
4. The protein of claim 3, wherein
(a) A3 is selected from the group consisting of
Glu-Ala-Lys,
Glu-Arg-Lys,
Glu-Pro-Lys,
Glu-Lys-Lys,
Glu-Ile-Thr,
Glu-His-Arg,
Glu-Leu-L;s, and
Glu-Thr-Lys;
(b) A4 is an amino acid sequence having a net anionic charge;
(c) A7 is Val or Ile;
(d) A8 includes an amino acid sequence selected from the group consisting of
```

```
A8.sub.a -A6.sub.b -31/-Phe-Tyr-Arg-Asp (SEQ. ID. NO. 78),
A8.sub.a -A8.sub.b -Gly-Phe-Tyr-Arg-Ash [SE]. II. NO. 19],
A8.sub.a -A8.sub.b -Gly-Tyr-Tyr-Arg-Asp [SE]. II. NI. +[],
A8.sub.a -A6.sub.b -Gl/-T/r-T/r-Arg-Ash [SE]. ID. Ni. +1], and
A8.sub.a -A8.sub.b -Gly-leu-Tyr-Arg-Asp (SE). II. NJ. 62),
wherein at least one of A.sup.f.sub.a and Af.suc.b is 31u or Asf;
 e' A9 is an amino abid sequence of five amino arid residues; and
 for All includes an amino acid sequence selected from the group consisting it
Glu-Ile-Ile-His-Val [CRY, II. NO. 194
Asp-Ile-Ile-Met-Val [SEQ. II. NO. 78
Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and
Met-Glu-Ile-Ile-Thr [SEQ. ID. NO.
5. The protein of claim 4 having a MAP domain substantiallly the same as a MAP domain
selected from the group consisting of AcaNAP5 [SEQ. ID. NO. 40], AcaNAP6 [SEQ. ID. NO. 41], AcaNAP4 [SEQ. ID. NO. 41], AcaNAP48 [SEQ. ID. NO. 42], AcaNAP43 [SEQ. ID. NO. 44], AcaNAP44 [SEQ. ID. NO. 44], AcaNAP44 [SEQ. ID. NO. 46], AcaNAP41 [SEQ. ID. NO. 47], AcaNAP44 [SEQ. ID. NO. 50 or 53], AcaNAP47 [SEQ. ID. NO. 51 or 54], AduNAP7 [SEQ. ID. NO. 52 or 56], AduNAP4 [SEQ. ID. NO. 55], AcaNAP5 [SEQ. ID. NO. 57], and AcaNAP7 [SEQ. ID. NO. 58],
6. An isolated protein having anticpagulant activity and having one or more NAP
dimains, wherein each NAP domain includes the sequence:
Dys-Al-Dys-A2-Cys-A3-Dys-A4-Dys-A5-Dys-A6-Dys-A7-Dys-A8-Dys-A9-Cys-A10 (FORMULA V),
wherein
.a) Al is an amino abid sequence of 7 to 8 amino abid residues;
(c) All is an amino acid sequence;
 a) AB is an amino acid sequence of B amino acid residues;
 d) A4 is an amino acid sequence;
 e: At is an amin: acid sequence of 3 to 4 amin: acid residues;
 f | Ad is an amin: adia sequence;
(g) AT is an amin: acid residue:
\chi \hat{\mathbf{h}}) A5 is an amino acid sequence of 11 to 12 amino acid residues;
(1) A9 is an amino acid sequence of 5 to 7 amino acid residues; and
(1) AlO is an amino acid sequence;
wherein each A2, A4, A6 and A10 has an independently selected number of independently
selected amino acid residues and each sequence is selected such that each NAP domain
has in total less than about 120 amino acid residues, and wherein said NAP domain
includes the amino acid sequence:
dys-Al-dys-A2-dys-A3-dys-A4-dys-A5-dys-A6-dys-A7-dys-A7-dys-A8-dys-A9-dys-A10,
(a) Cys-Al is selected from SEQ.II.NOS. 87 and 308;
(b) Cys-Al-Cys is selected from one of SEQ.ID.NOS. 309 to 311;
(c) A3-Cys-A4 is selected from one of SEQ.ID.NOS. 312 to 325;
(d) Cys-A5 is selected from SEQ.ID.NOS. 326 and 327;
.e) Cys-A6 is selected from one of SEQ.II.NGS. 328 to 330;
.f) Cys-A7-Cys-A8 is selected from SEQ.IE.NG3. 331 to 332;
\langle q \rangle Cys-AM is selected from one of SEQ.ID.NGS. 333 to 333; and
(h) Cys-AlO is selected from one of SEQ.ID.NOS. 556 to 356.
F. An isolated protein of claim 1 whereir Af has the sequence Glu-A3.sub.a -A3.sub.b
wherein A.s.p.S.sub.a and A3.sub.b are independently selected amino acid residues.
t. An isclated protein of claim 7 where A3.sub.a is selected from Ala, Arg, Pro, Lys,
lie, His, Leu and Thr and A3.sub.b is selected from Lys, Thr and Arg.
2. An isolated protein of claim 3 wherein A? is selected from the group consisting of
Glu-Ala-Lys, Glu-Arg-Lys, Glu-Pro-Lys, Glu-Lys-Lys, Glu-Ile-Thr, Glu-His-Arg,
Glu-Leu-Lys and Glu-Thr-Lys.
10. An isolated protein of claim 1 wherein A4 is an amino acid sequence having a net
artionic charge.

    Ar. isolated protein of claim 1 wherein A7 is Val or Ile.

11. An isolated protein of claim 1 wherein AB includes the amino acid sequence:
A8.sub.a -A3.sub.b -A3.sub.c -A8.sub.d -A8.sub.e -A8.sub.f -A8.sub.g (SEQ. ID. NO.
66 wherein
a. Af.sub.a is the first amino acid residue in A8; and
(b) at least one of A8.sub.a and A8.sub.b is selected from Glu and Asp; and
(c) Af.sub.c through A.sup.8.sub.g are independently selected amino acid residues.
13. An isolated protein of plaim 12 wherein
(a) A8.sulp. - is Gly;
(b) A8.sub.d is selected from Phe, Tyr and Leu;
(a) A8.sub.e is Tyr;
(d) A8.sub.f is Ard; and
(e) A8.sub.a is Asp or Asp.
```

```
14. An isolated protein of blaim 13 wherein Af.sub.c -Af.sub.d -Af.sub.f -Af.sub.g is
selected from one of SEQ. ID. NOS. 69 to 73.
15. An isclated protein of claim 1 wherein A13 includes an amino acid sequence
selected from one of SEQ. ID. NOS. 74\ TO\ 77 .
16. An isolated protein of claim 15 wherein AlC includes SEQ. ID. NO. 74.
17. An isolated protein according to claim 1 wherein
a) A3 has the amino acid sequence Glu-A3.sub.a -A3.sub.b wherein A3.sub.a and
A3. sub.b are independently selected amino acid residues;
(c) A4 is an amino acid sequence naving a net anionic charge;
 b) AT is selected from Val and Ile;
 d) At includes an amino acid sequence selected from one of SEQ. ID. NOS. 69 to 73;
ar.d
 e) AlO includes an amino abid sequence selected from one of SEQ. IO. NOS. 74 to ^{\circ\circ}.
14. An isolated protein according to claim 17 having one or two NAP domains. 14. An isolated protein according to claim 17 having one NAP domain. 14. An isolated protein according to claim 17 having one NAP domain. 15. An isolated protein of claim 1 wherein
(a) A3 is selected from the group consisting of Glu-Ala-Lys, Glu-Arg-Lys,
Glu-Pro-Lvs, Glu-Lvs-Lvs, Glu-Ile-Thr, Glu-His-Ard, Glu-Leu-Lvs and Glu-Thr-Lvs;
(b) A4 is an amino acid sequence having a net anichic charge;
+c) A is Val or Ile;
(d) A6 includes an amino acid sequence selected from one of SEQ. ID. NOS. 78 to 82;
(e) A9 is an amino acid sequence of five amino acid residues; and
(f) AlO includes an amin: acid sequence selected from one of SEQ. ID. NOS. 74 to 77.
21. An istlated protein of plaim 20 having one or two NAP domains.
22. An isplated protein of plaim 20 having one NAP domain.
23. An isolated protein of claim I wherein A3 has the amino acid sequence
Asp-A3.sub.a -A3.sub.b wherein A3.sub.a and A3.sub.p are independently selected amino
acid residues.
24. An istlated protein of claim 35 wherein A5 is Asp-Lys-Lys.
15. An isolated protein of claim 2 wherein A4 is an amino acid sequence having a net
amionic charge.
26. An isolated protein according to plaim 2 wherein A5 is A5.sub.a -A5.sub.b
-A5.sub.c -A5.sub.d (SEQ. IP. NO. 84) and wherein A5.sub.a through A5.sub.b are
independently selected amino acid residues.
27. An isolated protein according to plaim 16 wherein A5.sub.a is Leu and A5.sub.c is
Arq.
18. An istlated protein addording to claim I wherein A7 is Val or Ile.
19. An isolated protein according to claim 18 wherein A7 is Val.
31. An isolated protein according to claim , wherein A\delta includes the amino acid
sequence A8.sub.a -A8.sub.b -A8.sub.c -A8.sub.d -A8.sub.e -A3.sub.f -A8.sub.g (SEQ.
ID. NO. 68) wherein
(a) A8.sub.a is the first amino acid residue in A8;
(b) at least one of A8.sub.a and A8.sub.b is selected from Glu and Asp; and
(c) A8.sub.c through A.sup.8.sub.q are independently selected amino acid residues.
31. An isolated protein according to claim 30 wherein
(a) A8.sub.c is Gly;
(b) A8.sub.d is selected from Phe, Tyr and Leu;
(c) A8.sub.e is Tyr;
(d) A8.sub.f is Arg; and
(e) A.sup.8.sup.d is selected from Asp and Asn.
32. An isolated protein according to claim 31 wherein A8.sub.c -A8.sub.d -A8.sub.e
-A8.sub.f -A8.sub.q is SEQ. ID. NO. 70.
33. An isolated protein of claim I wherein
(a) A3 has the amino acid sequence Asp-A3.sub.a -A3.sub.b wherein A3.sub.a and
All sub.b are inderendently selected amino anid residues;
r) A4 is an amino acid sequence having a net anionic charge;
is) AS has the amino asid sequence AS.sub.a -AS.sub.b -AS.sub.c -AS.sub.d (SEQ. ID.
NV. 85) wherein Af.sub.a through A5.sub.d are independently selected amino acid
residues; and
(a) A7 is selected from Val and Ile.
34. An isolated protein of claim :3 having one or two NAP domains.
35. An isolated protein of claim 33 having one NAP domain.
36. An isolated protein of claim 2 in wherein
a) A5 is Asp-Lys-Lys;
h) A4 is an amino acid sequence having a net anionic charge;
[3] AE has the amino acid sequence A5.sub.a -A5.sub.b -A5.sub.c -A5.sub.d (SEQ. ID.
No. 85) wherein Af.sub.a through Af.sub.d are independently selected amino acid
residues;
```

(d) A7 is Val; and

```
(e) A8 includes the amino acid sequence A8.sub.a -A8.sub.b -31y-Fhe-Tyr-Ard-A8n SE,.
ID. MG. 79' wherein at least one of Ab.sub.a and Ab.sub.b is Gla or Asp.
37. An isolated protein of claim 36 having one or two NAF domains.
38. An isolated protein of claim 36 having one NAF domain.
19. An isolated protein of claim 3 wherein Ab has the amino which sequence
dlu-Af.sub.a -Ad.sub.b wherein Af.sub.a and Af.sub.b are independently selected anima
word residues.
40. An isolated protein of claim 39 wherein A3 is 31u-Pro-Lys.
41. An isclated protein of claim 3 wherein A4 has a net anichic charge.
42. An is:lated protein of claim 3 wherein AS has the amino acid sequence Ab.suc.a
-A5.sub.p -A5.sub.c wherein A.sup.8.sub.a through A5.sub.c are independently selected
amino acia residues.
43. An istlated protein of claim 40 wherein A.sup.S.sup.a is Thr and AD.sub.c is Asn.
44. An istlated protein of blaim 43 wherein A5 is Thr-Lwu-Asm th
Thr-Met-Asn.
45. An isolated protein of claim 3 wherein AT is Glu.
4%. An isolated protein of claim 3 wherein.
.a) AS has the sequence of Glu-A3.sub.a -A3.sub.b wherein A3.sub.a and A3.sub.b are
independently selected amino acid residues;
(h) A4 is an amino acid sequence having a net anionic charge;
ು) At has the sequence At.sub.a -At.sub.b -At.sub.c whereir At.sub.a to At.sub.c are
independently selected amino acid residues; and
 a) A7 is Glu.
47. An isplated protein of claim 46 having one or two NAP domains.
48. An isolated protein of claim 46 daving one MAS domain.
49. An isslated protein of claim 3 wherein
(a) A3 is Glu-Pro-Lys;
(n) A4 is an amino abid sequence having a net anionic charge;
(a) A5 is selected from Thr-Leu-Ash and Thr-Met-Ash; and
(a) A7 is Glu.
50. An isolated protein of claim 49 having one or two NAP domains.
51. An isolated protein of claim 49 having one NAP domain.
E2. An isolated protein of claim 6 wherein A3 has the sequence G1u-A3.sub.a -A3.sub.b
wherein AB. sub.a and AB. sub.b are independently selected amino acid residues.
53. An isolated protein of claim 52 wherein Al.sub.a is selected from Ala, Arg, Pro,
Lys, Ile, His, Let and Thr and A3.sub.b is selected from Lys, Thr and Arg.
64. An isolated protein of plaim 63 wherein A3 is selected from Glu-Ala-Lys,
Glu-Arg-Lys, Glu-Pro-Lys, Glu-Lys-Lys, Glu-Ile-Thr, Glu-His-Arg, Glu-Leu-Lys and
G.u-Thr-Lys.
ff. An isolated protein of plaim 6 wherein A4 is an amino acid sequence having a net
anionic charge.
50. An isolated protein of plaim 6 wherein A7 is Val or Ile.
57. An isolated protein of claim \ell wherein AE includes the amino acid sequence
A8.sub.a -A8.sub.b -A8.sub.c -A8.sub.a -A8.sub.e -A8.sub.f -A8.sub.g (SEQ. ID. NO.
65) wherein
(a) A8.sub.a is the first amino apid in A8;
b) at least one of A8.sub.a and A8.sub.b is selected from Glu and Asp; and
 a) A8.sub.s and A8.sub.s are independently selected amino acid residues.
58. An isolated protein of plaim 57 Amerein
(a) A8.sub.c is Gly;
(b) A8.sub.d is selected from Phe, Tyr and Leu;
(c) A8.sub.e is Tyr;
(a) A8.sub.f is Arg; and
(e) A8.sub.q is selected from Asp and Asr.
59. An isplated protein of claim 58 wherein Af.sub.c -A8.sub.d -A8.sub.e -A8.sub.f
-A3.sub.; is selected from SEQ. ID. NOS. 69 to 73.
60. An isolated protein of claim 6 wherein All includes an amino acid sequence
selected from SEQ. ID. NOS. 74 to 7%.
61. An isolated protein of claim \boldsymbol{\theta} wherein
(a) A3 has the amino acid sequence Glu-A3.sub.a -A3.sub.b wherein A.sup.3.sub.a and
AB.sub.b are independently selected amino acid residues;
•b) A4 is an amino acid sequence having a net anionic charge;
(a) A7 is selected from Val and Ile;
(c) A8 includes an amino acid sequence selected from SEC. II. Not. (2007) and
(e) AlO includes ar amino acid sequence selected from SED. II. W.C. 14 ***
62. An isolated protein of claim (1 having are or two NAE praims) 63. An isolated protein of claim (1 having are NAE a main)
64. An isolated protein of claim of naving two MAF d mains.
```

```
65. An isolated protein of claim 6 wherein
(a) A3 is selected from Glu-Ala-Lys, Glu-Arg-Lys, Glu-Pro-Lys, Glu-Lys-Lys,
Glu-Ile-Thr, Glu-His-Arg, Glu-Leu-Lys and Glu-Thr-Lys;
(b) A4 is an amino acid sequence having a net anionic charge;
(c) A7 is Val or Ile;
(d) A8 includes an amino acid sequence selected one of SEQ. ID. NOS. 78 to 82;
(e) A9 is an amino acid sequence having five amino acid residues; and
(f) Al( includes an amino acid sequence selected from one of SEQ. ID. NOS. 74 to 77.
66. An isolated protein of claim 65 having one or two NAP domains.
67. An isolated protein of claim 65 having one MAP domain.
68. An isolated protein of claim 66 having two NAP domains.
69. An isolated protein of draim of having two has remained.
69. An isolated protein having anticoagulant and/or serine protease inhibitory activity and having one or more NAF domains, wherein each NAF domain includes the sequence Cys-A.sub.1 -Cys-A.sub.2 -Cys-A.sub.4 -Cys-A.sub.6 -Cys-A.sub.6 -Cys-A.sub.7 -Cys-A.sub.6 -Cys-A.sub.7 -Cys-A.sub.6 -Cys-A.sub.7 -Cys-A.sub.6 -Cys-A.sub.1 is an amino acid sequence containing 1 to a amino acid residues;
(c) A.sub.3 is an amino acid sequence containing 1 to 5 amino acid residues;
(d) A.sub.3 is an amino acid sequence containing 6 to 7 amino acid residues;
(d) A.sub.4 is an amin: acid sequence containing 6 to 7 amino acid residues; (e) A.sub.5 is an amin: acid sequence containing \tilde{\epsilon} to 4 amino acid residues;
(f) A.sub.6 is an amino acid sequence containing 3 to 5 amino acid residues;
(a) A.sub.7 is an amino acid residue;
(\hat{\mathbf{h}}) A.sub.8 is an amino acid sequence containing 10 to 12 amino acid residues; and
(i) A.sub.9 is an amino acid sequence containing 0 to 6 amino acid residues;
and wherein said NAP domain includes the amino acid sequence
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys, wherein
(a) Cys-Al is selected from SEQ. ID. NOS. 60 and 129;
(b) Gys-A2-Gys is selected from one of SEQ. ID. NOS. 130 to 133;
(a) A3-Cys-A4 is selected from one of SEQ. ID. NOS. 134 to 145;
(d) Cys-A5 is selected from one of SEQ. ID. NOS. 146 and 147;
(e) Cy-A6 is selected from one of SEQ. ID. NOS. 148 to 150;
(f) Cys-A7-Cys-A8 is selected from one of SEQ. ID. NOS. 151 to 153; and
(g) Cys-A9-Cys is selected from SEQ. ID. NOS. 184 and 158.
78. An isolated protein of claim 69 wherein
(a) Cys-A2-Cys is selected from SEQ. IO. NOS. 131 and 131; and
(b) A3-Cys-A4 is selected from one of SEQ. ID. NOS. 135 to 145.
71. An isolated protein of claim 71 having a MAP domain wherein
(a) SEQ. II. NOS. 66 and 129 have 3lu at location 6;
(b) SEQ. II. NOS. 130 and 131 have Gly at location 0;
(c) SEQ. IF. NOS. 151 to 153 have Gly at location 6 and Arg at location 9; and
(d) SEQ. ID. NOS. 154 and 155 have Val at location 2.
72. An isolated protein of claim 71 having a NAP domain wherein SEQ. ID. NOS. 151 to
153 have an amino acid sequence which includes (a), (b) and/or (c) wherein
(a) is Val or Glu at location 2;
(b) is Leu or the at location 7; and
(c) is Lys or Tyr at location δ.
73. An isolated protein of claim 71 having a MAP domain wherein
(a) SEQ. ID. NO. 151 has Asp or Gly at location 14;
(b) SEQ. II. NO. 152 has Asp or Gly at location 13; and
(c) SEQ. ID. NO. 153 has Gly at location 13.
```